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March 11, 1999

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket 98D-0994-BACPAC I: Intermediates in Drug Substance Synthesis

Dear Sir or Madam:

As a US Representative, SST Corporation presently markets over 100 API and intermediates in the United States produced by pharmaceutical manufacturers worldwide, including but not limited to Fabbrica Italiana Sintetici, Erregierre SpA., Zambon Group SpA., Unique Pharmaceutical Laboratories, Neuland Laboratories Limited, USV Limited and Dixie Chemical Company, Inc.. In conjunction with these manufacturers, we feel the BACPAC I draft guidance represents a positive, initial step towards improving post approval filing requirements. Specifically, we whole-heartedly support the goal of providing less burdensome filing of selected post approval changes falling within the scope of 21CFR 314.70 (a). Furthermore, we support the Agency's desire for a data-driven BACPAC as the foundation to establish that pre and post change material is equivalent (lines 81-84).

The BACPAC I Guidance is an improvement for an NDA/ANDA sponsor(s) for changes in site, scale, equipment and specifications. Unfortunately, it provides little or no relief for Holders of Type II Drug Master Files, i.e. those mentioned above. The Draft also falls short of clear, decisive, proportional, data-driven guidance in the specific area of Process Change.

As the simplest way to summarize our comments, we have attached decision trees which illustrate what we feel are the most appropriate filing mechanisms for BACPAC I changes. The filing mechanisms presented are in complete agreement with the central tenet of the guideline with respect to equivalence and propose a proportional response to any given change. These decision trees differ from the one offered in the Guidance in that they are specific to each type of change and they lead the reader to either a filing mechanism or to anticipating the future BACPAC II Guidance. In each decision tree, we have highlighted any points that differ from those presented in the Guidance.

In addition, we would like to offer the following comments:

98D-0994

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1. Equivalence: We fully support the statement beginning on line 81, “A central tenet of this guidance is that a given change in the drug substance manufacturing process can be adequately accessed by comparing pre and post change materials and demonstrating that the post change material is equivalent to the pre change material.” It is clear that this tenet demands a data-driven BACPAC. However, the Guidance then proceeds to *pre-determine* the filing mechanism based on the *potential* impact of certain criteria. For example, line 442, recommends a CBES filing using the criteria that all intermediates and starting materials are the same. This pre-judges the situation before obtaining the data. It may be that a more or less restrictive filing mechanism is needed, depending upon the *actual* impact of the process change which only the data can reveal. For example, if equivalence were shown before the Final Intermediate, an Annual Report would seem more appropriate than a CBES (please refer to our Process Change Decision Tree); conversely, if the data reveals that equivalence cannot be shown until the API itself, a PAS/CBES filing would seem appropriate (please refer to our Process Change Decision Tree).

Although the nature of the process change needs to be known, it is not the defining issue. *For process changes, the location of the equivalence point is the essential attribute that defines the actual impact of the change.* This is determined only by obtaining and evaluating the data. Once this is known, a filing mechanism can be applied based upon the known impact of the change; i.e. a restrictive one for a change with major impact and a less restrictive one for a change with minor impact.

2. Manufacturing Process Changes: For changes in the route of synthesis in one or more steps involving different starting materials and/or intermediates (line 480), the most stringent filing mechanism, a prior approval supplement (PAS) for the ANDA/NDA sponsor (s) is recommended. However, this fails to consider that equivalency may have been determined upstream from the API. This should make a PAS unnecessary. A PAS filing mechanism needs to be applied to changes that have a maximum impact; i.e. those which require equivalence to be shown at the drug substance itself and not in an upstream intermediate. Regardless of the location of the process change, when equivalence needs to be determined at the drug substance itself; a PAS/CBES should be the appropriate filing mechanism since the data has shown the change has had a maximum impact (please refer to our Process Change Decision Tree). Similarly, if equivalence is already determined upstream, i.e. at or before the final intermediate, a less restrictive filing mechanism should logically follow, i.e. annual report (please refer to our Process Change Decision Tree).

We also feel a distinction should be made between the terms “manufacturing change” and “process change” with the combination term “manufacturing process change” (line 399 and others) eliminated. We recommend “manufacturing change” refer to all the changes discussed, i.e., site, scale, equipment, specification and process, whereas, “process change” is only one type of a manufacturing change. Combining the terms seems unnecessarily complicated. Unless this distinction is made, it will not be clear whether a “manufacturing change” means a process change or is referring to all the other types of changes. These definitions should be included in the glossary.

3. Agency Meetings: Line 480 and following reads “For route changes very early in the synthetic scheme where equivalence is determined soon after the change, submission as a changes being effected supplement may be justified. In those situations, the appropriate review division(s) should be contacted for concurrence prior to filing.” This guidance contradicts a key objective of the BACPAC Guidance, namely to offer more efficient filing of post approval changes. Industry is looking to BACPAC to issue a clear, decisive guidance so that all firms, large or small, Generic or Innovator, can file process (and other) changes without requiring numerous meeting with the Agency. This is important since a large international pharmaceutical firm has more resources to interact with the Agency than a smaller one. If one needs to meet with the Agency to determine whether a PAS or CBES is necessary, BACPAC I has not issued decisive guidance.

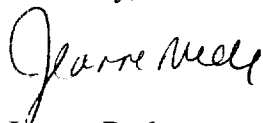
4. Filing for DMF Holders: Line 73 reads, “If the method of manufacture is described in a master file, then documentation of the modification should be filed as amendment(s) to the master file...”. This idea is reiterated in each “Type of Change” section with the statement “Test Documentation filed as an amendment to the master file(s) and/or in an annual report or supplement to the application(s) as appropriate”. Hence it appears that the only filing mechanism available to the DMF holder is the amendment, even if the sponsor(s) is filing by Annual Report.

Clarification is needed as to why the Agency has not mandated Annual Update on the part of the DMF Holder as the companion filing mechanism for Annual Report on the part of the DMF Holder. This lack of guidance has significant implications in the multi-customer environment of a generic API manufacturer.

We trust the FDA will consider these ideas and will recognize the need to resolve the above issues for regulatory filings on bulk post-approval changes. As written, this Guidance does not provide an adequate amount of relief in the area of process changes. This is especially critical since API manufacturers need to be able to make beneficial process changes without a disproportionate regulatory burden that overwhelms this effort; the central goal of a BACPAC Document. These process changes will ultimately benefit society in general (and patients specifically) by providing more efficient, economical and environmentally friendly processes than are presently being utilized.

Thank you for the opportunity to respond to this Draft Guidance. We look forward to future Agency/Industry dialogue on this critical subject. Perhaps another Workshop such as the one in March '97 may be appropriate.

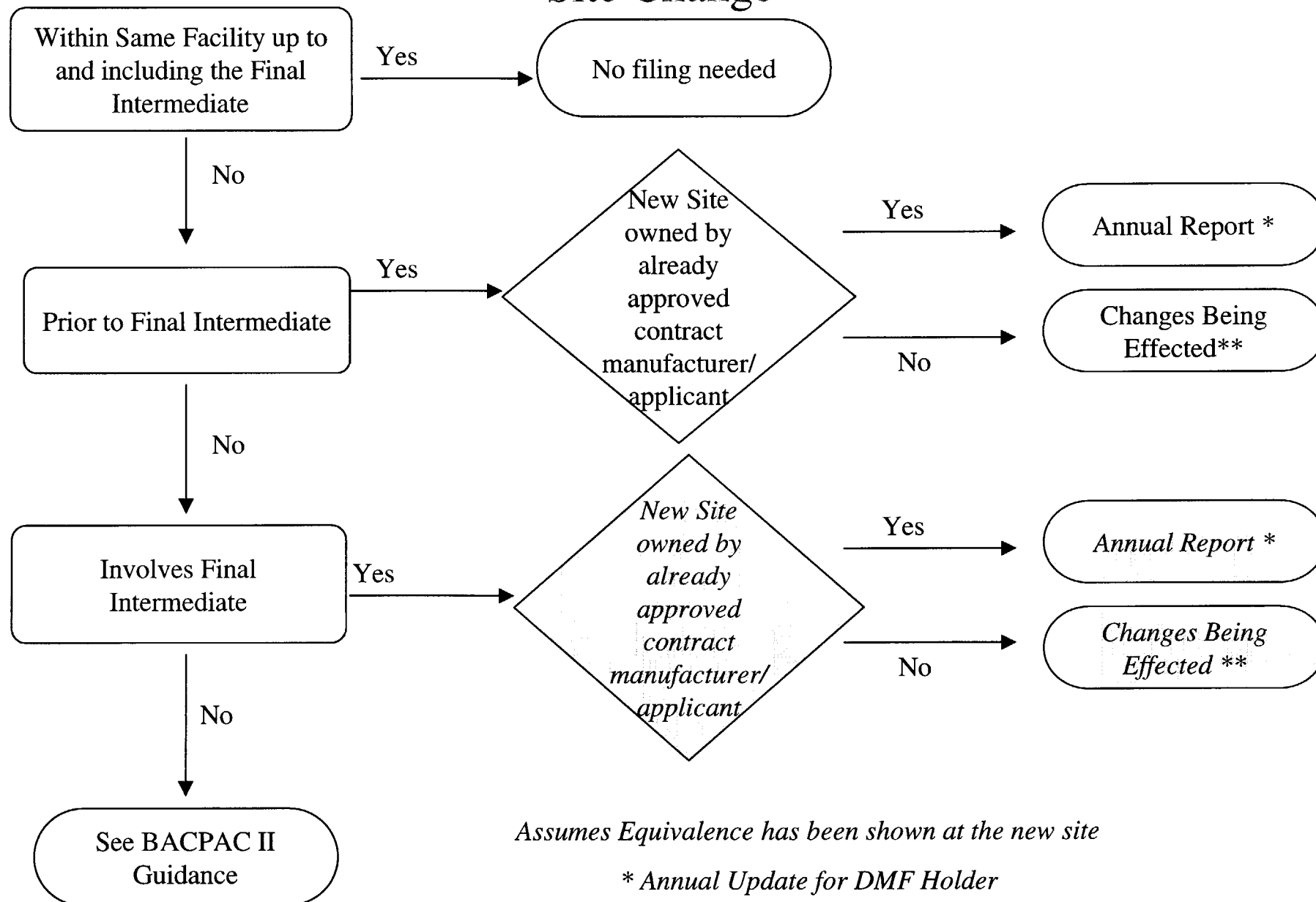
Sincerely,



Jeanne Rude
Manager, Regulatory and Technical Affairs

CC: Arthur Fabian, Ph.D., Kathleen Dougherty

Site Change

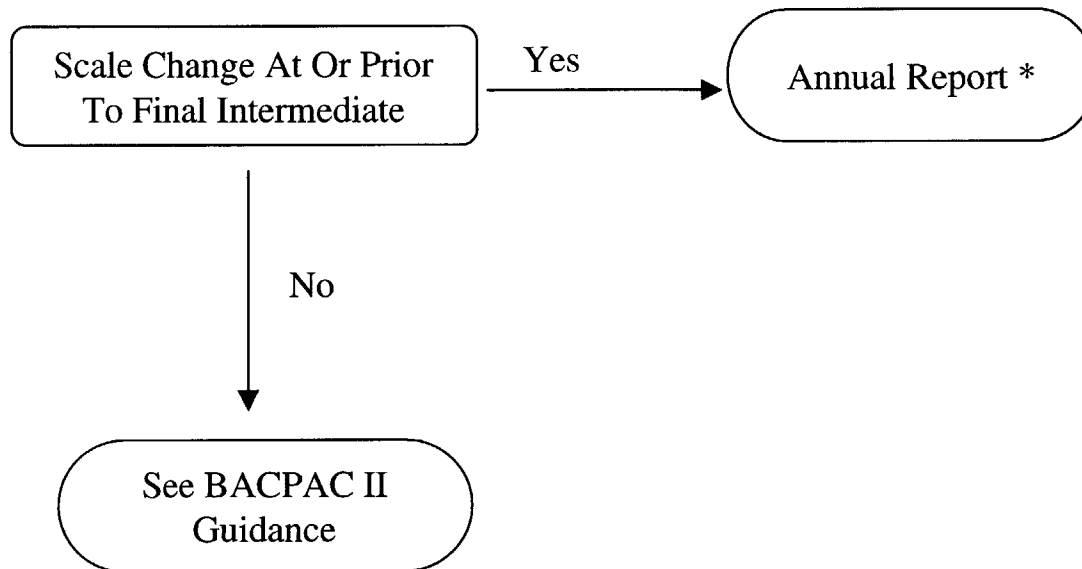


Assumes Equivalence has been shown at the new site

** Annual Update for DMF Holder*

*** Amendment for DMF Holder*

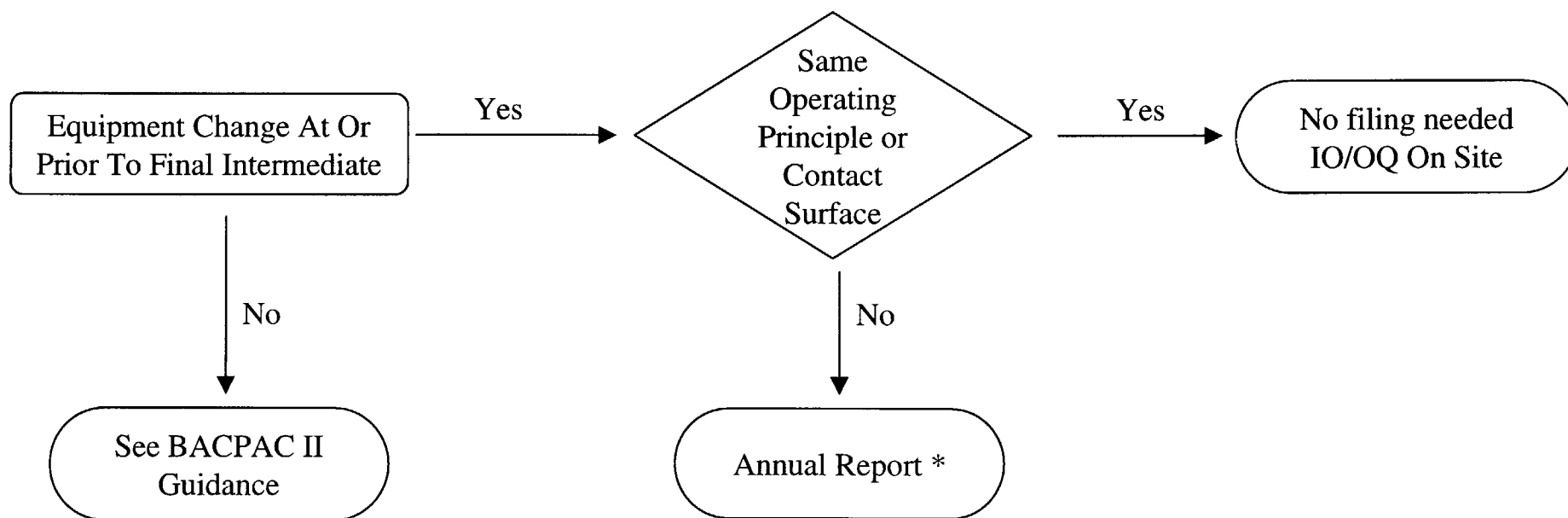
Scale Change



Assumes Equivalency Has Been Shown

** Annual Update for DMF Holder*

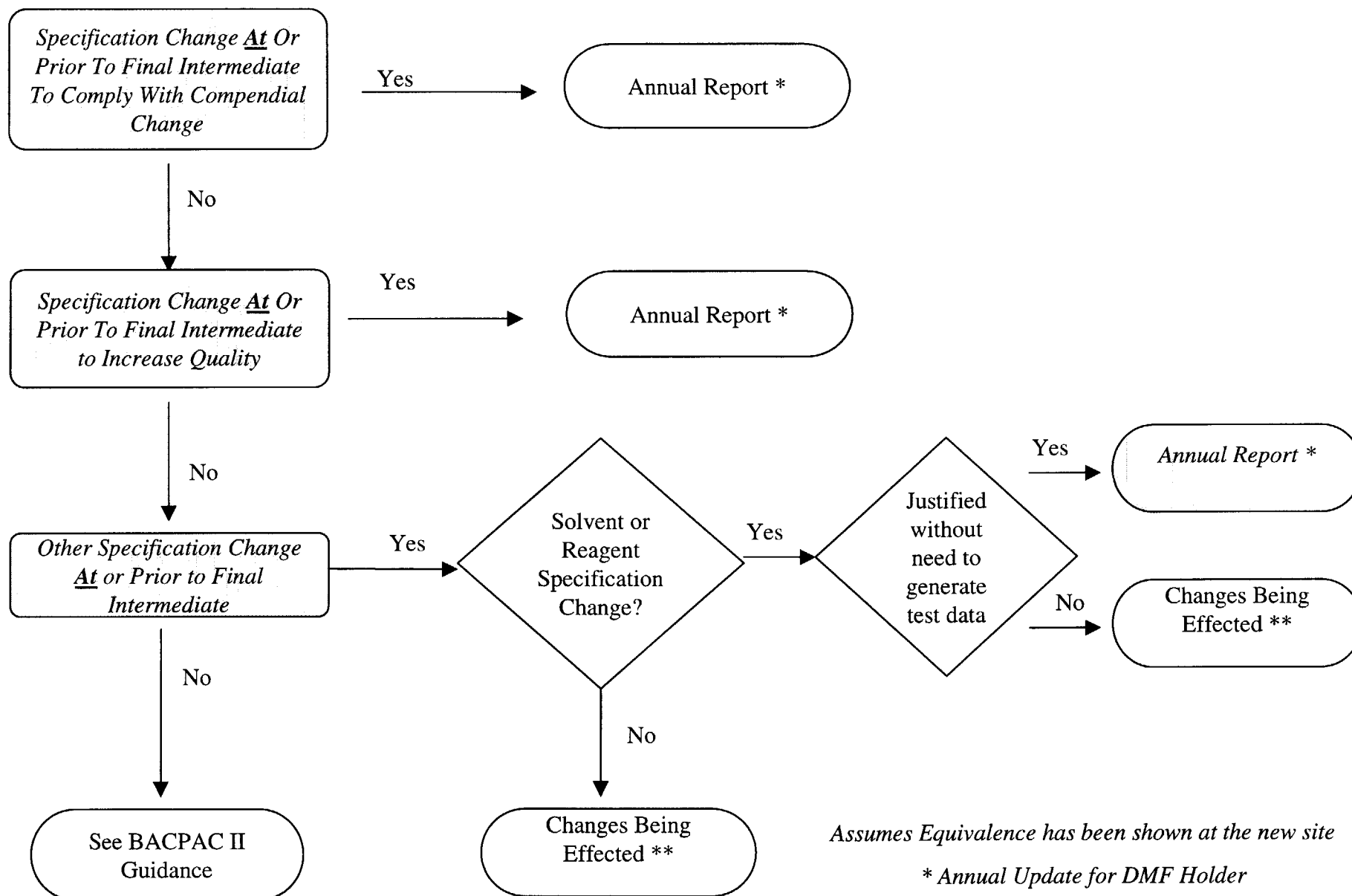
Equipment Change



Assumes Equivalency Has Been Shown

** Annual Update for DMF Holder*

Specification Change (for Raw Materials, Starting Material or Intermediates)

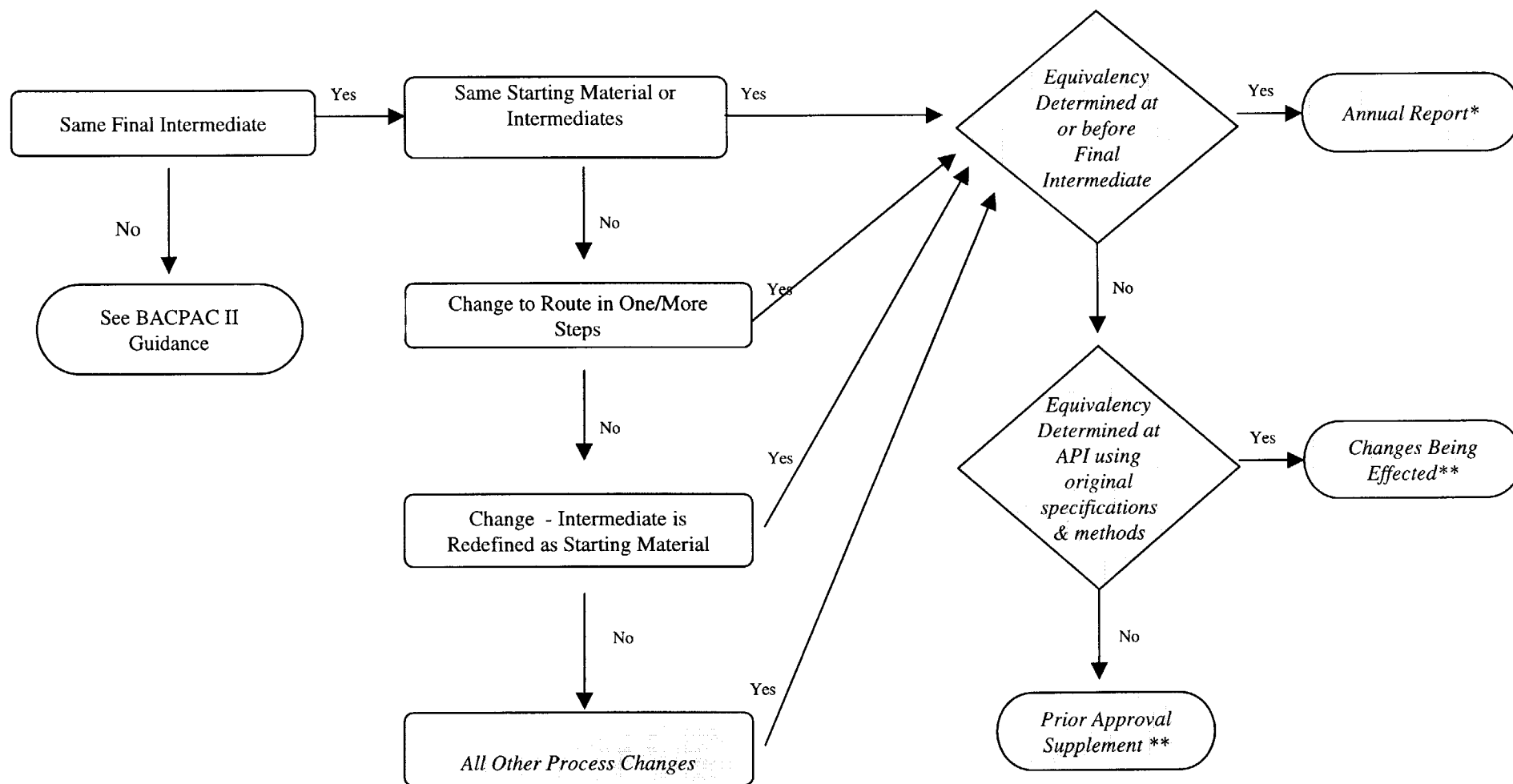


Assumes Equivalence has been shown at the new site

** Annual Update for DMF Holder*

*** Amendment for DMF Holder*

Process Change



Assumes Equivalence has been shown at the new site

** Annual Update for DMF Holder*

*** Amendment for DMF Holder*